different melting point than microcapsules of a second [portion] group of said microcapsules, and further wherein both first and second melting points are lower than the Curie point of the magnetic particles.

(6) In claim 71, line 1, please replace the word "portion" with --group--; likewise in claim 71, line 2, please replace the word "portion" with --group--.

REMARKS

In response to the Office Action dated July 30, 1999, Applicant respectfully submits the amendments above and the remarks below for the Examiner's consideration.

Claims 1-59 and 60-68 are pending; claims 1, 3, 4, 5, and 69 are amended.

I. Priority Date Under 35 U.S.C. § 120

The Examiner has stated that Applicants have not complied with one or more conditions for receiving the benefit of the earlier filing date of the parent application, now U.S. Patent No. 5,827,531. The Examiner found that the application failed to teach "a microcapsule comprising energy absorbing components such as graphite, aluminum powder or TWEEN, or drugs such as anesthetics, antiparasites, or antibiotics such as erythromycin, or gentamycin." The Examiner also found that the application did not teach the claimed method of controlled drug delivery to a patient, or the claimed method of treating a tumor.

Applicants respectfully disagree. This application is a continuation-in-part of the parent application and was filed May 15, 1998 before the parent U.S. Patent No. 5,827,531 issued. This continuation-in-part application ("CIP") was filed during the lifetime of the parent application by the same applicants, repeated a substantial portion of the earlier application, added matter not disclosed in the earlier case, and references the parent application.

MPEP 201.08 states that a continuation-in-part application should be permitted to claim the benefit of the filing date of an earlier application if:

1. The parent and CIP were filed with at least one common inventor;

2. The CIP was filed before the patenting or abandonment of the parent; and

3. The CIP contains a specific reference to the earlier filed application.

The present application has met all of the requirements necessary to claim the benefit of the filing date of its parent U.S. Patent No. 5,827,531 and Applicants request that the Examiner withdraw this rejection.

The Applicants also respectfully disagree that the CIP fails to teach the claimed invention with regard to:

1. *Microcapsules comprising energy absorbing components such as graphite, aluminum powder or TWEEN*. Example XI on page 62, lines 3-9, and page 63, lines 6-11, of the disclosure clearly identifies graphite particles, aluminum and a combination of TWEEN, sodium amyl alcohol and paraffin oil as primary energy absorbers.

2. *Microcapsules comprising drugs such as anesthetics, antiparasites, or antibiotics*. The patent application references the use of such compounds in several places, as for example on page 10, lines 22-24.

3. *Method of controlled drug delivery*. The disclosure teaches the claimed method of controlled drug delivery at various places in the application such as on page 9, lines 9-27, page 10, lines 1-17, page 40, lines 7-26, and pages 43-46.

4. *Method of treating a tumor*. Although the disclosure teaches the claimed method of treating a tumor in several places such as on page 11, lines 13-23; Applicants submit that claims 60-68 were withdrawn from consideration due to a restriction requirement and are no longer pending in this application.

II. Rejection under 35 U.S.C. § 112

Claims 3 and 4 stand rejected for failing to have sufficient antecedent basis for "energy absorbing medium." In response, Applicants have amended claims 3 and 4 to recite "energy absorbing component" which has sufficient antecedent basis in claim 1.

Claim 5 stands rejected under 35 USC 112, second paragraph as being indefinite for its recitation of "at least internal hydrocarbon phase." In order to clarify claim 5, "at least internal hydrocarbon phase" has been amended to read -- at least one internal hydrocarbon phase --.

Claim 69 stands rejected under 35 USC 112, second paragraph as being indefinite because of reference to "the first portion" and "the second portion" of the microcapsules. The claim has been amended to clarify that the composition comprises a number of microcapsules and that the microcapsules of one group of those capsules has an outer membrane with a different melting temperature than the microcapsules of at least one other group of the microcapsules.

III. Rejection under 35 U.S.C. § 102

A. Mathiowitz et al US Patent 4,898,734

Claims 1, 7, 21, 40, 44, 51-52, and 56-59 stand rejected as being anticipated by Mathiowitz et al US Patent 4,898,734 (hereinafter referred to as Mathiowitz).

Applicants respectfully traverse the Examiner's reasoning. Invalidity for anticipation requires that there is no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

Independent claim 1 and its dependent claims 7, 21, and 40 recite one or more energy absorbing components in an internal liquid phase having a higher specific absorption rate for magnetic, radiofrequency, microwave, or ultrasound than the specific absorption rate of the polymer membrane. This limitation in claim 1 reflects the encapsulation of a selected energy absorbing component within the microcapsules that will preferentially absorb energy. Since the energy absorbing component is in contact

with the outer membrane it will melt at least a portion of the outer membrane in a manner dependent on the selection of the energy absorbing component and its specific absorption rate.

In contrast, Mathiowitz does not encapsulate an energy absorbing component with a particular specific absorption rate in a liquid phase to produce a material for the controlled absorption of energy. Mathiowitz depends on the biodegradation of the microcapsular membrane or the rupture of the microcapsular membrane with temperature, light or ultrasound. (see Abstract and column 5, lines 21-40). The rupture of the microcapsular capsule with temperature, light or ultrasound is a direct action of the energy on the outer membrane, rather than an indirect action mediated through an energy absorbing compound as claimed in the present invention.

Independent claim 44 and its dependent claim 51-52 and 56-59 recite a method for controlling the release of a drug. Claim 44, like claim 1, recites drug delivery microcapsules having one or more energy absorbing components in an internal liquid phase in contact with the outer membrane, where the energy absorbing component has a higher specific absorption rate for magnetic, radiofrequency, microwave, or ultrasound than the specific absorption rate of the polymer membrane. The drug is release by the selective administration of an energy source to heat the energy absorbing component to melt the outer membrane and release the drug.

As described above, Mathiowitz teaches the rupture of microcapsular outer membranes directly, rather than relying on a separate compound in the microcapsule to absorb energy, melt the outer membrane and release the drug. Mathiowitz's microcapsules all have the same outer membrane, thus all of the drug would be released at one time. Whereas, the present invention contemplates the inclusion of different energy absorbing components in different microcapsules, whereby one can selectively release various groups of the microcapsules by judiciously selecting the energy absorbing components and their specific absorption rate. The teachings of the present invention allow one to selectively release different drugs at different localized temperatures and/or to release different fractions of the same drug at different times to control the sustainable release of the drug(s). Mathiowitz is discussed in more detail below.

B. Radhakrishnan US Patent 5,049,389

Claims 1-3, 6-10, 13-16, 30-35, and 40 stand rejected as being anticipated by Radhakrishnan US Patent 5,049,389 (hereinafter referred to as Radhakrishnan).

Applicants respectfully disagree with the Examiner. Independent claim 1 and its dependent claims 2-3, 6-10, 13-16, 30-35 and 40 recite one or more energy absorbing components in an internal liquid phase having a higher specific absorption rate for magnetic, radiofrequency, microwave, or ultrasound than the specific absorption rate of the polymer membrane. This limitation in claim 1 reflects

the encapsulation of a selected energy absorbing component within the microcapsules that will preferentially absorb energy. Since the energy absorbing component is in contact with the outer membrane it will melt at least a portion of the outer membrane the outer membrane in a manner dependent on the selection of the energy absorbing component and its specific absorption rate.

Radhakrishnan encapsulates drugs for delivery to the deep lung. Radhakrishnan does not encapsulate an energy absorbing component used to melt the outer membrane, but purely relies on the partitioning of the drugs from the liposomal bilayer to the cell membrane in the lung. (see Example V, column 25-26, particularly column 25,lines 44-55). In addition, Radhakrishnan states that "the cholesterol ester salt and cholesterol are mandatory components of the nonconventional liposomes formulation and are not interchangeable with phospholipids." (see column 18, lines 48-56). Radhakrishnan's nonconventional liposomes are totally based upon partitioning coefficients of the drugs to be delivered and therefore Radhakrishnan teaches a different construction of microcapsules that has nothing to do with energy absorption or energy absorbing components. Radhakrishnan is discussed in more detail below.

C. Unger et al US Patent 5,853,752

All claims were rejected by the Examiner as being anticipated by Unger et al US Patent 5,853,752 (hereinafter referred to as Unger).

Applicants respectfully traverse the Examiner's reasoning. Unger, like Mathiowitz and Radhakrishnan, does not teach the encapsulation of an energy absorbing component that is specifically heated to a temperature beyond the melting point of the outer membrane by the absorption of energy. Independent claims 1, 41, 44 and 69 each contain limitations related to temperature. Amended claim 1 recites "wherein the temperature of said energy absorbing component is increased by absorbing said energy to melt at least a portion of the polymer membrane." Claim 41 recites at least two groups of microcapsules, each group containing a magnetic particle with a Curie point that is different from the Curie point of the magnetic particle in the other group and where the Curie point of all magnetic particles is higher than the melting temperature of the polymer membrane. Claim 44 recites "exposing the microcapsules to an energy source, effective to heat the internal component and to melt at least a portion of the polymer outer membrane and to release the drug." Amended claim 69 recites at least two groups of microcapsules, each having an outer membrane with a different melting point and where each melting point is less than the Curie point of the magnetic particles.

Unger does not teach the use of temperature to control the release of drug. At column 29, lines 59-67, Unger actually teaches away from the use of higher wattage and time because of the increased

heating. Rather than encapsulating an energy absorbing component to control the heating of a component to melt the outer membrane, Unger teaches the coordination of membrane composition with peak resonant frequency of a gaseous precursor to rupture the liposomes. For example, column 25, lines 15-22, states "liposomes prepared from dipalmitoylphosphatidylcholine are most preferred as they are selected for their ability to rupture on application of resonant frequency ultrasound, radiofrequency energy, (e.g. microwave), and/or echogenicity . . . ." This statement taken in conjunction with Unger's teaching of applying ultrasound at the peak resonance frequency of the therapeutic gaseous precursor-filled liposomes (see column 29, lines 31-41), clearly demonstrates that Unger teaches the selection of the liposomal membrane components to provide the rupture properties for the delivery of drugs based on the gaseous precursor's peak resonance frequency. Thus, the rupture of the Unger liposomes is governed by the makeup of the liposomal membrane and the gaseous precursor, not the energy absorption rate and increased temperature of an encapsulated energy absorbing component. A more detailed discussion of Unger is set out below.

IV. Rejection under 35 U.S.C. § 103

Claims 1-43 and 69-71 were rejected by the Examiner as being unpatentable over Mathiowitz, Grinstaff et al US Patent 5,508,021, Radhakrishnan and Unger. Of the claims held to be unpatentable by the Examiner, claims 1, 41, and 69 are independent claims.

The Applicants disagree with the Examiner's rejection of these claims for all the reasons stated above, as well as those outlined below.

Independent Claim 1.

Amended claim1, requires that "said energy absorbing component having a higher specific absorption rate for magnetic, radiofrequency, microwave or ultrasound energy than the specific absorption rate of the polymer membrane, wherein the temperature of said energy absorbing component is increased by absorbing said energy to melt at least a portion of the polymer membrane."

A. Mathiowitz

As stated above, Mathiowitz does not teach the inclusion of an energy absorbing component with a higher specific energy absorption rate than the polymer membrane. Mathiowitz teaches the rupture of microcapsules based on the specific energy absorbent rate of the polymer membrane itself not the melting of the outer membrane by a heated energy absorbing component. Mathiowitz discloses that "substances to be released can be dissolved in the embedding polymer, dissolved into the polymer forming the microcapsule or microsphere, or encapsulated within the microcapsules." (see column 5,

lines 54-57). Mathiowitz teaches that "the matrix and microcapsule polymers rupture upon exposure to a presclected temperature, thereby releasing the carbon tetrachloride." (see column 6, lines 1-4).

Mathiowitz's discloses two release mechanisms. One mechanism is based on the rupture of the matrix or the microcapsule polymers, not the melting of a portion of the polymer membrane based on the selective heating of an energy absorbing component that is in contact with the outer membrane. "Temperature release is obtained by heating the microcapsules." (see column 5, lines 15-16) Mathiowitz's temperature release involves heating the entire microcapsule to rupture the outer membrane. Thus this mechanism involves the heating of the surrounding tissue and is not localized by heating specific energy absorbing components. The other mechanism is based on biodegradable microcapsules, not the specific melting of the microcapsules. Mathiowitz does not suggest or motivate one to encapsulate an energy absorbing component with a higher specific absorption rate than the specific absorption rate of the polymer membrane.

B. Grinstaff et al US Patent 5,508,021 ("Grinstaff")

Grinstaff discloses enclosing imaging agents in polymeric shells. Grinstaff teaches the inclusion of paramagnetic cations such as Gd, Mn, Fe, and the like as an effective MRI contrast agent. (column 5, lines 21-24). The term "imaging agent" is defined as any compound or combination of compounds which enhance the visualization of organs and other cellular structures from the surrounding medium. (see column 5, lines 46-49). For example, Grinstaff discusses "altering the local magnetic field by introducing small iron particles . . . to provide proton differentiation." The use of paramagnetic cations to induce proton differentiation is a total different use than to use them for specifically absorbing energy to increase their temperature.

Grinstaff does discuss the use of imaging agents that are capable of undergoing a phase transition over physiological temperature ranges so that MRI can be used to measure local temperatures. (see column 9, lines 28-67, and column 10, lines 1-11). Such materials would be totally unsuitable as energy absorbing compounds, since they are selected to fulfill their mission at physiological temperatures. The microcapsules of the claimed invention require that the energy absorbing component have a higher specific absorption rate than the outer membrane such that its temperature is increased by absorbing energy so as to melt at least a portion of the polymer membrane. Grinstaff does not suggest or motivate one to encapsulate an energy absorbing component with a higher specific absorption rate than the specific absorption rate of the polymer membrane as a mechanism for melting a portion of the outer membrane.

C. Radhakrishnan

Radhakrishnan discloses a non-conventional lipid particle formulation for the sustainable release and delivery of drugs, particularly steroids, into the deep areas of the lung. Radhakrishnan discloses the preparation of liposomes that release the encapsulated drug by absorption into the cell or based on the partitioning of the drugs from the liposomal bilayer to the cell membrane in the lung. (see Example V, column 25-26, particularly column 25,lines 44-55). Radhakrishnan's invention relies on the composition of the outer membrane and the partitioning of the drug within that membrane. For example, Radhakrishnan states that "the cholesterol ester salt and cholesterol are mandatory components of the nonconventional liposomes formulation and are not interchangeable with phospholipids." (see column 18, lines 48-56). Radhakrishnan's nonconventional liposomes are totally based upon partitioning coefficients of the drugs to be delivered and therefore Radhakrishnan teaches a different construction of microcapsules that has nothing to do with energy absorption or the melting of a portion of the outer membrane by selectively heating an energy absorbing component that is in contact with the outer membrane. Radhakrishnan does not suggest or motivate one to encapsulate an energy absorbing component with a higher specific absorption rate than the specific absorption rate of the polymer membrane.

D. Unger

Unger, as discussed above, does not teach the use of a selected localized temperature to melt the outer polymer membrane. Unger teaches the use of gaseous precursor-filled liposomes in ultrasonic imaging and drug delivery systems. Unger actually teaches away from the use of increased temperatures as a means of rupturing the liposomes. Instead of temperature, Unger teaches the use of "adjusting the frequency of the energy to match the peak resonant frequency" of the gaseous precursor-filled liposomes to rupture the liposomal membrane and to avoid appreciable tissue heating. (see column 29, lines 64-67). Since Unger liposomes are based on rupture by peak resonant frequency, it is important that membrane constituents be used that will rupture on the application of resonant frequency ultrasound, radiofrequency energy and/or echogenicity. (see column 29, lines 31-41).

Furthermore, Unger teaches the use of gaseous filled liposomes rather than liquid filled liposomes.

At column 33, lines 47-54, Unger discloses the use of paramagnetic gases as contrast agents for MRI. As mentioned above, this is a totally different use of these agents from their use as an energy absorbing component pursuant to the present invention. Unger does not suggest or motivate one to

encapsulate an energy absorbing component with a higher specific absorption rate than the specific absorption rate of the polymer membrane.

Independent Claim 41.

Claim 41 requires microcapsules comprising two or more internal liquid phases enclosed with polymer outer membranes, where one or more magnetic particles are included in the liquid phases in contact with the outer membrane. Claim 41 also recites that a portion of the microcapsules have magnetic particles with a different Curie point than the magnetic particles in another portion of the microcapsules.

The only discussion of magnetic particles in the patents cited by the Examiner was in the context of the inclusion of paramagnetic materials as contrast agents for MRI. See the discussion of Grinstaff and Unger above. The use of paramagnetic materials in MRI to provide proton differentiation is extremely different than using magnetic particles to preferentially absorb energy to increase the temperature of those magnetic particles. Not one of the references hint, suggest or discuss the use of magnetic particles to specifically absorb energy for melting the outer membrane. Nor do any of the references discuss the use of more than one such material in the liposomes or microcapsules, as is claimed in claim 41.

Independent Claim 69.

Amended claim 69 recites a composition of at least two groups of microcapsules, where the microcapsules of a first group have an outer membrane with a different melting temperature than the microcapsules of the second group and where both melting points are lower than the Curie point of the magnetic particles.

Not one of the cited patents discusses the advantages of multiple groups of microcapsules with outer membranes having different melting points, nor is there any suggestion that one should encapsulate one or more magnetic particles having a Curie point that is higher than the melting point of the microcapsular membranes. Mathiowitz does not suggest or motivate one to encapsulate an energy absorbing component with a higher specific absorption rate than the specific absorption rate of the polymer membrane.

V. Dependent Claims

Claims 2-40 depend on independent claim 1, claims 42-43 depend on independent claim 41, claims 45-59 depend on independent claim 44, and claims 70-71 depend on independent claim 69. Since

the dependent claims contain all of the limitations of the independent and intervening claims, the Examiner's rejection of claims 2-40, 42-43, 45-59, and 70-71 is obviated for the reasons set forth above with respect to independent claims 1, 41, 44 and 69.

VI. Combination of References

None of the cited references suggest or even hint at the encapsulation of at least one energy absorbing component to preferentially absorb energy to increase the energy absorbing component's temperature such that it can melt a portion of the outer plasma membrane of microcapsules to release a drug. The preferential heating of the energy absorbing component bestows a number of advantages on the present invention and solves existing problems in controlled drug delivery. For example the localized heating of the energy absorbing component does not require that the tissue targeted for treatment will undergo the same temperature increase, thereby protecting the tissue from extensive damage due to increased temperature. In addition, the present invention allows one to specifically design more than one group of microcapsules that can be injected into, or otherwise delivered to, a target site for sustained delivery of a drug or the controlled release of multiple drugs. Not one of the references provide motivation or impetus to produce the microcapsules of the present invention.

None of the cited papers, alone or in combination, would render Applicants' invention obvious. The Federal Circuit has clearly stated that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984). The Federal Circuit has stated that it is improper to use the claims of an invention as a framework upon which to conceptually assemble elements of prior references without some motivation to do so. The Applicants contend that there is nothing in the cited references or prior art that would have suggested or even hinted at producing microcapsules containing energy absorbing components to absorb energy and thereby increase the temperature of the energy absorbing component to selectively melt at least a portion of the outer membrane of specific microcapsules for the controlled release of drugs.

According to *In re Margolis*, 228 U.S.P.Q. 940,942 (Fed. Cir. 1986), in determining obviousness, the Examiner must consider the advantages of a claimed invention when those advantages are set out in the specification. In this case, the Applicants have clearly pointed out the advantage of creating microcapsules containing energy absorbing components with higher specific absorption rates for an energy source than the specific absorption rate of the outer microcapsular membrane. *In re Wright*, 6 U.S.P.Q.2d 1959,1961 (Fed. Cir. 1988) requires that consideration of "invention as a whole" (as required by Section 103) incorporate a consideration of the particular problem addressed by the inventors.

Consideration of Applicants' invention as a whole, including the purpose and the problems addressed by the inventors demonstrates the non-obviousness of the invention.

In view of the foregoing amendments and remarks, it is respectfully submitted that Applicants have responded in a fully satisfactory manner to all matters at issue in this application.

Should the Examiner have any questions or suggestions concerning the application or allowance of any claim thereof, or feels that an interview would advance the examination process, the Examiner is requested to call the Applicants' undersigned attorney at the direct dial number printed below.

Respectfully,

James M Cate

James M. Cate

Registration No. 25181

NASA Johnson Space Center
Mail Code: HA
Houston, Texas 77058
Telephone: (281) 483-1003

I hereby certify that this correspondence is addressed to The Assistant Commissioner for Patents, Washington, D.C. 20231, and is being deposited with the United States Postal Service with sufficient postage as First Class Mail on October 21 1999.

James M Cate

James M. Cate